DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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August 6, 2014

THE BINDING SITE GROUP LTD
C/O MS SUZANNE HORNE, REGULATORY AFFAIRS MANAGER
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BIRMINGHAM, WEST MIDLANDS B15 1QT
United Kingdom

Re: K140686
Trade/Device Name: Hevylite Human IgM Kappa Kit For Use On SPA_{PLUS}®
Hevylite Human IgM Lambda Kit For Use On SPA_{PLUS}®
Regulation Number: 21 CFR 866.5510
Regulation Name: Immunoglobulins A, G, M, D, and E immunological test system
Regulatory Class: II
Product Code: PDE, PDF
Dated: July 04, 2014
Received: July 07, 2014

Dear Ms. Horne:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the

electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Maria M. Chan -S

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K140686

Device Name
Hevylite Human IgM Kappa Kit for use on SPAPLUS
Hevylite Human IgM Lambda Kit for use on SPAPLUS

Indications for Use *(Describe)*
Hevylite Human IgM Kappa kit for use on SPAPLUS is intended for the in-vitro quantification of IgM kappa (combined μ heavy and κ light chain) concentration in human serum on the Binding Site SPAPLUS. The test result is to be used with previously diagnosed Waldenström's macroglobulinaemia in conjunction with other clinical findings.
This assay has not been established for the diagnosis, monitoring and prognosis of Waldenström's macroglobulinaemia.

Hevylite Human IgM Lambda kit for use on SPAPLUS is intended for the in-vitro quantification of IgM lambda (combined μ heavy and λ light chain) in human serum on the Binding Site SPAPLUS. The test result is to be used with previously diagnosed Waldenström's macroglobulinaemia. The test result is to be used in conjunction with other clinical findings.
This assay has not been established for the diagnosis, monitoring and prognosis of Waldenström's macroglobulinaemia.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Maria M. Chan -S

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Hevylite® Human IgM Kappa and IgM Lambda Kits for use on SPAPLUS®

510(k) Summary

Version: 5th August 2014

Contact Information:
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Trade Names:
Hevylite® Human IgM Kappa Kit for use on SPAPLUS®
Hevylite® Human IgM Lambda Kit for use on SPAPLUS®

Classification Names:

Product Classification Code	Product Code Name	Device Class	Classification Panel	21 CFR Section
PDE	Immunoglobulin M Kappa Heavy and light chain combined	II	Immunology	866.5510
PDF	Immunoglobilin M Lambda heavy and light chain combined	II	Immunology	866.5510

Intended use:
Hevylite Human IgM Kappa Kit for use on SPAPLUS is intended for the *in vitro* quantification of IgM Kappa (combined μ heavy and k light chain) concentration in human serum on SPAPLUS. The test result is to be used with previously diagnosed Waldenström's macroglobulinaemia in conjunction with other clinical and laboratory findings.
This assay has not been established for the diagnosis, monitoring and prognosis of Waldenström's macroglobulinaemia.

Hevylite Human IgM Lambda Kit for use on SPAPLUS is intended for the *in vitro* quantification of IgM Lambda (combined μ heavy and λ light chain) concentration in human serum on SPAPLUS. The test

result is to be used with previously diagnosed Waldenstrom's macroglobulinaemia in conjunction with other clinical and laboratory findings.
This assay has not been established for the diagnosis, monitoring and prognosis of Waldenström's macroglobulinaemia.

Test Principle:

Evaluating the concentration of a soluble antigen (e.g. IgM Kappa and IgM Lambda) by turbidimetry involves the addition of the test sample to a solution containing the appropriate antibody (anti-IgM kappa and anti-IgM lambda) in a reaction vessel or cuvette. A beam of light id passed through the cuvette and, as the antigen-antibody reaction proceeds, the light passing through the cuvette is scattered increasingly as insoluble immune complexes are formed. Light scatter is monitored by measuring the decrease in intensity of the incident beam of light. The antibody in the cuvette is in excess so the amount of immune complex formed is proportional to the antigen concentration. A series of calibrators of known antigen concentration are assayed initially to produce a calibration curve of measured light scatter versus antigen concentration. Samples of unknown antigen concentration can then be assayed and the results read from the calibration curve.

Substantial Equivalence Information:

Predicate device: **Hevylite** Human IgM Kappa and IgM Lambda Kits for use on Siemens BN™II Systems (k113823)

Comparison with Predicate:

Similarities

Item	Device	Predicate
Intended use	*In-vitro* quantification of IgM kappa and IgM Lambda	*In-vitro* quantification of IgM kappa and IgM Lambda
Specimen Type	Serum	Serum
Antibody	Sheep anti-IgM kappa and anti-IgM lambda coated onto polystyrene latex	Sheep anti-IgM kappa and anti-IgM lambda coated onto polystyrene latex
Open Vial Stability	1 month	1 month

Differences

Item	Device	Predicate
Standard Measuring range	IgM Kappa: 0.2 -5.0g/L (1/10) IgM Lambda: 0.18 – 4.50g/L (1/10)	IgM Kappa: 0.2 – 6.4g/L (1/100) IgM Lambda: 0.175 – 5.60g/L (1/100)
Reference Interval	IgM Kappa: 0.19 – 1.63g/L IgM Lambda: 0.12 – 1.01g/L IgM Kappa/Lambda: 1.18 – 2.74	IgM Kappa: 0.29 – 1.82g/l IgM Lambda: 0.17 – 0.94g/L IgM Kappa/Lambda: 0.96 – 2.30
Method	Turbidimetry	Nephelometry
Instrument	Binding Site SPAPLUS	Siemens Behring Nephelometer II (BN™II)

Discussion:

The differences between the methods of the devices do not affect the safety and effectiveness as they both measure light scatter, the only difference is where the detector is in the path of the light source.

The differences in the measuring ranges do not affect the safely and effectiveness as they both have the same lower limit and any results >5.0g/L on the kappa kit and >4.5g/L on the lambda kit will not have a clinical impact on patients if the results were quantified on the BN™II kit or reported as >5.0g/L on the kappa kit and >4.5g/L on the lambda kit.

The differences in the reference intervals do not affect the safety and effectiveness as the measuring ranges for the SPAPLUS kits were generated and the measuring ranges on the BN™II kits were from literature with different samples. The comparison data shows that the results obtained on both sets of kits are equivalent to each other.

Performance Characteristics:

Analytical performance:

Precision/Reproducibility:

The precision study was based on CLSI (EP5-A2) Evaluation of Precision Performance of Quantitative Measurement Methods. Precision was initially evaluated using three samples of processed sera pooled with fully preserved citrate beta alanine that together had analyte levels that spanned measuring range of the assays (IgM Kappa 0.2 – 5.0g/L, IgM Lambda: 0.18 – 4.50g/L).

The 21 day precision study was performed by running the sera samples in duplicate (within-run analysis), two runs per day (between-run analysis) over 21 days (between-day) using three reagent lots (Batches 1, 2 and 3) and four instruments (SPAPLUS 2, 5, 7 and 9).

An additional "bridging" precision study was carried out. Precision was evaluated using five samples of pooled native sera that together had analyte levels that spanned the measuring range of the assays (IgM Kappa 0.2 – 5.0g/L, IgM Lambda: 0.18 – 4.50g/L). A summary of the precision samples used are described below:

The 21 day bridging precision study was performed by running the sera samples in duplicate (within-run analysis), two runs per day (between-run analysis) over 21 days (between-day) using one reagent lot and three instruments (SPAPLUS 1, 9 and 12).

Repeatability

Initial IgM Kappa (Data present in IFU):

Sample	N	Mean	Within Run		Between run		Between day		Total		Pass? (CV<8%)
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	
High Level	84	4.13	0.08	1.8	0.08	1.8	0.21	4.6	0.24	5.3	Pass
Mid Level	84	1.80	0.03	1.5	0.03	1.3	0.66	3.5	0.08	4.1	Pass
Low Level	84	0.34	0.01	2.4	0.01	3.3	0.02	4.9	0.02	6.4	Pass

IgM Bridging Study:

Sample	N	Mean (g/L)	Within Run		Between run		Between day		Total		Pass? (CV<8%)
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	
1	84	0.34	0.01	1.8	0.01	2.7	0.01	3.2	0.02	4.6	Pass
2	84	1.13	0.16	1.4	0.03	2.3	0.02	1.9	0.03	3.3	Pass
3	84	1.89	0.28	1.8	0.04	2.3	0.07	4.6	0.08	5.4	Pass
4	84	4.50	0.04	0.9	0.07	1.5	0.09	2.1	0.12	2.8	Pass
5	84	5.20	0.05	1.0	0.11	2.1	0.14	2.5	0.19	3.5	Pass

Initial IgM Lambda (Data present in IFU):

Sample	N	Mean	Within Run		Between run		Between day		Total		Pass? (CV<8%)
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	
High Level	84	4.11	0.07	1.7	0.06	1.5	0.18	4.4	0.20	5.0	Pass
Mid Level	84	0.96	0.02	1.9	0.01	0.6	0.03	3.2	0.03	3.8	Pass
Low Level	84	0.29	0.01	2.0	0.01	2.1	0.02	5.4	0.02	6.1	Pass

IgM Lambda Bridging Study:

Sample	N	Mean (g/L)	Within Run		Between run		Between day		Total		Pass? (CV<8%)
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	
1	84	0.26	0.01	2.0	0.01	3.3	0.01	4.1	0.01	5.7	Pass
2	84	0.71	0.01	1.3	0.02	3.0	0.00	0.0	0.02	3.3	Pass
3	84	1.22	0.01	1.0	0.07	5.8	0.00	0.0	0.07	5.9	Pass
4	84	3.86	0.05	1.3	0.16	4.2	0.10	2.6	0.20	5.1	Pass
5	84	5.24	0.06	1.1	0.34	6.5	0.19	3.6	0.39	7.5	Pass

Reproducibility

Initial IgM Kappa Data:

Sample	Mean (g/L)	# Runs	# Days	Within-Run		Between-run		Between-Instrument		Between-Batch		Total		Pass? (CV<8%)
				SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %	
High Level	4.13	2	21	0.08	1.8	0.08	1.8	0.15	3.6	0.22	5.4	0.24	5.3	Pass
Mid Level	1.80	2	21	0.03	1.5	0.03	1.3	0.06	3.1	0.06	3.3	0.08	4.1	Pass
Low Level	0.34	2	21	0.01	2.4	0.01	3.3	0.01	3.8	0.00	0.3	0.02	6.4	Pass

IgM Kappa Bridging Study:

Sample	Mean (g/L)	# Runs	# Days	Within-Run		Between-run		Between-Instrument		Total		Pass? (CV<8%)
				SD	CV%	SD	CV%	SD	CV%	SD	CV%	
1	0.34	2	21	0.01	1.8	0.01	2.7	0.01	2.7	0.02	4.6	Pass
2	1.13	2	21	0.16	1.4	0.03	2.3	0.02	1.9	0.03	3.3	Pass
3	1.89	2	21	0.28	1.8	0.04	2.3	0.07	3.6	0.08	5.4	Pass
4	4.50	2	21	0.04	0.9	0.07	1.5	0.07	1.6	0.12	2.8	Pass
5	5.20	2	21	0.05	1.0	0.11	2.1	0.07	1.3	0.19	3.5	Pass

Initial IgM Lambda Data:

Sample	Mean (g/L)	# Runs	# Days	Within-Run		Between-run		Between-Instrument		Between-Batch		Total		Pass? (CV<8%)
				SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV%	
High Level	4.11	2	21	0.07	1.7	0.06	1.5	0.16	3.9	0.11	2.7	0.20	5.0	Pass
Mid Level	0.96	2	21	0.02	1.9	0.01	0.6	0.03	3.4	0.02	2.3	0.03	3.8	Pass
Low Level	0.29	2	21	0.01	2.0	0.01	2.1	0.02	5.0	0.01	3.3	0.02	6.1	Pass

IgM Lambda Bridging Study:

Sample	Mean (g/L)	# Runs	# Days	Within-Run		Between-run		Between-Instrument		Total		Pass? (CV<8%)
				SD	CV%	SD	CV%	SD	CV%	SD	CV%	
1	0.26	2	21	0.01	2.0	0.01	3.3	0.01	4.7	0.01	5.7	Pass
2	0.71	2	21	0.01	1.3	0.02	3.0	0.01	0.8	0.02	3.3	Pass
3	1.22	2	21	0.01	1.0	0.07	5.8	0.02	2.0	0.07	5.9	Pass
4	3.86	2	21	0.05	1.3	0.16	4.2	0.14	3.5	0.20	5.1	Pass
5	5.24	2	21	0.06	1.1	0.34	6.5	0.33	6.3	0.39	7.5	Pass

Linearity/assay reportable range:

The linearity of the assays was assessed using one lot of reagent on one analyser.

The high pools for IgM kappa and IgM Lambda were prepared from a serum sample with a naturally high concentration of IgM kappa and adjusted by the addition of purified IgM. A low pool for IgM kappa was prepared from a normal serum sample adjusted with the addition of IgM depleted serum. The low pool for IgM Lambda was prepared from IgM depleted serum. A dilution series was prepared for IgM kappa and IgM lambda separately by blending the respective high and low pool (described above); to produce a total of 12 concentrations (described below) that covered the measuring range of the assays. Three replicates of each level of the dilution series were run and the mean calculated.

An additional study was performed to evaluate the bottom of the standard measuring range for IgM Kappa. A high pool was prepared from pooled normal human serum and diluted with IgM depleted serum to provide samples with a concentration range of 0.086 – 0.405g/L.

Linearity was evaluated by calculating the percentage recovery at each concentration in the dilution series, and the %CV of the 3 replicates. The acceptance criteria was a mean recovery of ≤±10%, or an acceptable recovery of ≤±16.8% and a CV of <8%. Linearity was demonstrated at the concentrations spanning the claimed measuring range. The observed values were graphed against the calculated values and a linear regression was performed.

The regression plot equations where y is the measured level of IgM kappa or lambda and x is the theoretical concentration were:

Sample	Dilution Range (g/L)	Regression equation	Slope (95% CI)	Y-Intercept (95% CI)	R
IgMκ Sample	0.158 – 5.911	y = 1.00x + 0.02	1.00 (0.97 to 1.03)	0.02 (-0.08 to 0.12)	0.999
	0.086 – 0.405	y = 1.02 – 0.00	1.02 (0.95 to 1.08)	0.00 (-0.02 to 0.01)	0.997
IgMλ Sample	0.131 – 5.085	y = 0.97x + 0.02	0.97 (0.96 to 0.99)	0.02 (-0.03 to 0.07)	1.00

The approximate measuring range of the **Hevylite** Human IgM Kappa kit for use on the SPAPLUS is 0.2 – 5.0g/L.

The approximate measuring range of the **Hevylite** IgM Lambda kit for use on the SPAPLUS is 0.18 – 4.50g/L.

Linecision:

The precision and accuracy of the SPAPLUS analysers' instrument dilution function, a "linecision" study was carried out on one analyser and one reagent lot.

Two serum samples with target analyte concentrations falling in the overlapping regions between the measuring ranges of each instrument dilution. Each sample was run with 20 aspirations against each instrument measuring range (1/1, 1/10, 1/90).

An additional study was carried out to evaluate the manual pre-dilution step using 3 separate users. A third sample was targeted at the overlapping region between the 1/90 and 1/250 measuring ranges. The third sample was run with 20 aspirations against the 1/90 instrument dilution. When sample three was run at the 1/250 instrument dilution it was carried out by 3 operators who diluted the sample as per the product insert. That sample was then aspirated 20 times against the 1/250 instrument dilution.

The acceptance criteria were a recovery of ±10% for each sample and a CV of the 20 aspirations of ≤8%.

Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability

The calibrators, the master calibrator and controls are traceable to ERM-DA470k International Reference Material. The master calibrator is prepared from pooled human sera and is used to control calibration between lots.

Device Stability

Real-time stability studies were performed to support the following stability claims of the **Hevylite** IgM Kappa and **Hevylite** IgM Lambda kits:

- Shelf-life stability of the opened kits when stored at 2 - 8°C is up to 2 months.
- Shelf-life stability for unopened kits when stored at 2 - 8°C is 12 months.

Detection limit:

The limit of blank (LoB) and limit of detection studies were performed based on the protocol described in CLSI EP17-A. The detection limit was determined by testing a blank sample (IgM depleted serum), samples close to the bottom of the neat 1/1 measuring range (LoQ), and a sample with value close to the blank (LoD) sample at a neat sample dilution (1/1).

The LoB was determined non-parametrically by running the IgM depleted sample. The assigned concentrations were equivalent to 0.00g/L for both IgM Kappa and IgM Lambda as the sample was depleted of analyte. Samples were tested 60 times to determine LoB.

The LoQ samples were five serum samples that had a mean analyte concentration within ±10% of the bottom of the measuring range. The assigned concentrations were equivalent to the bottom of the neat measuring range (1/1), 0.02g/L for IgM kappa and 0.018g/L for IgM lambda. The five samples were tested 12 times each over 5 days for LoQ.

The LoD is the lowest measurable concentration of the analyte that can be distinguished from zero; it has been calculated as 0.0012g/L for IgM kappa and 0.0016g/L for IgM lambda for the minimum sample

dilution for the assay (1/1). LoD was determined from the LoB value (LoD = LoB + 1.645 SD_D where, SD_D is the pooled precision estimate of the LoQ study samples).

Analytical specificity:

Interfering Substances

Interference by endogenous substances were evaluated by addition of haemoglobin (5g/L), bilirubin (200mg/L), Intralipid (500mg/dL) and triglycerides (1000mg/dL) to test serum samples representing the analyte concentrations representing concentrations in the normal range, sample close to the lower medical decision point (LMDP), close to the upper medical decision point (UMDP), a low pathological sample and a high pathological sample. The negative control pools were prepared by spiking commercially obtained blank or saline when blank samples were not obtainable, into the sera base pools. Samples were tested three times each. The acceptance criteria was percentage difference of < ±10%. No significant interference was observed with the interferents tested.

Rheumatoid factor (RF) was not evaluated because this autoantibody is directed against the Fc portion of immunoglobulins. Interference is unlikely to take place in the **Hevylite** Human IgM kappa and IgM Lambda assays, as the Fc region of the anti-IgM kappa and anti-IgM lambda antibodies are cleaved prior to coating onto the latex bead.

The medical decision points are defined as the upper and lower limits of the normal reference range.

The package insert states in the Limitations section that “Turbidimetric assays are not suitable for measurement of highly lipaemic or haemolysed samples or samples containing high levels of circulating immune complexes (CICs) due to the unpredictable degree of non-specific scatter these sample types may generate. Unexpected results should be confirmed using an alternative assay method”.

Cross reactivity:

Cross reactivity studies were carried out by testing **Hevylite** IgM Kappa and **Hevylite** IgM Lambda assays in the presence of high concentrations of potentially cross reacting monoclonal proteins in samples from IgA1κ, IgA1λ, IgA2κ, IgA2λ, IgG1κ, IgG1λ, IgG2κ, IgG2λ, IgG3κ, IgG3λ, IgG4κ, IgG4λ, κ free light chain and λ free light chain multiple myeloma patient sera. No significant cross reactivity was observed.

The samples were all tested for total IgG, total IgA, total IgM, and also with the **Hevylite** IgM Kappa and IgM Lambda assays. The results for total IgM were compared with the results obtained by the **Hevylite** IgM Kappa and IgM Lambda assays.

In addition, IgMκ patient samples were tested on Hevylite IgM Lambda kits to investigate potential cross-reactivity, and similarly, IgMλ patient samples were tested on IgM kappa kits.

Antigen excess effect:

Prozone parameters are in effect to protect the SPAPLUS analyser from antigen excess effects. Reaction kinetics of high level samples was compared to that of the top calibrator for each kit. Samples detected as being in excess are flagged with a “P” flag.

Assay cut-off:

The cut-off values are the reference ranges for the normal population which have been established from the reference range study.

Comparison study:

Method comparison with predicate device:

A total of 227 and 269 sera samples spanning the range were assayed in singlicate on both Hevylite Human IgM kappa and IgM Lambda Kits for use on SPAPLUS respectively, these results were compared to those obtained on the Hevylite Human IgM Kappa and IgM Lambda Kits for use on Siemens BNII.

The serum samples included 41 Waldenström's Macroglobuliaemia patients, 23 normal donors and samples with elevated IgM Kappa and IgM Lambda levels. Passing and Bablok regression are based on the balance of the paired results:

IgM Kappa: y=0.84x + 0.07g/L

IgM Lambda: y= 0.93x + 0.00g/L

The percentage positive (abnormal result) and negative (normal result) agreement in the serum samples for each assay:

IgM Kappa	Predicate	
	Positive	**Negative**
Positive	159	2
Negative	11	55

Positive percentage agreement: 93.5% (88.7 to 96.7%)
Negative percentage agreement: 96.5% (87.9 to 99.5%)
Overall agreement: 94.3% (88.3 to 95.6%)

IgM Lambda	Predicate	
	Positive	**Negative**
Positive	131	2
Negative	16	120

Positive percentage agreement: 89.1% (82.9 to 93.7%)
Negative percentage agreement: 98.4% (94.2 to 99.8%)
Overall agreement: 93.3% (89.6 to 96.0%)

When considering the upper and the lower limits of the reference range as medical decision points for the IgM Kappa / IgM Lambda Ratio, the positive and negative agreement are as follows:

IgM Kappa/ IgM Lambda	Predicate	
	Positive	**Negative**
Positive	164	4
Negative	14	40

Positive percentage agreement: 92.1% (87.2 to 95.6%)
Negative percentage agreement: 90.9% (78.3 to 87.5%)
Overall agreement: 91.9% (87.5 to 95.1%)

Clinical Studies:

Clinical Sensitivity and Specificity:

Clinical cut-off:

Not applicable.

Expected values/ Reference range:

The normal ranges established in accordance with CLSI C28-A3 using 147 UK adult blood donors. The assays were performed on the SPAPLUS analyser. A non-parametric analysis of specimens for the distribution of IgMκ and IgMλ was performed.

Normal range results as included in IFU:

Normal adult serum	Mean	Median	95 Percentile Range
IgM kappa (g/L)	0.71	0.63	0.19 – 1.63
IgM lambda (g/L)	0.39	0.35	0.12 – 1.01
IgM kappa/ IgM lambda ratio	1.85	1.81	1.18 – 2.74

The upper and lower limits of the reference range for IgMκ (0.19 – 1.63g/L), IgMλ (0.12 – 1.01g/L) and the IgMκ/λ ratio (1.18 – 2.74) are defined as the "cut-offs". Samples with a **Hevylite** result above any of these reference ranges, or below the lower cut-off are classified as abnormal.

The cut-offs have been validated by comparing percentage agreement between the predicate device and the **Hevylite** IgM kappa and IgM **Lambda** kits.

Conclusion:

The **Hevylite** Human IgM Kappa and the **Hevylite** Human IgM Lambda kits for use on the SPAPLUS are substantially equivalent to the **Hevylite** Human IgM Kappa and IgM Lambda Kits for use on Siemens BN™II as they have the same intended use, technological characteristics, features and principles of operation as the **Hevylite** Human IgM Kappa and IgM Lambda Kits for use on Siemens BN™II that do not raise new questions of safety and effectiveness.

The validation data demonstrates that the performance characteristics also do not raise new questions of safety and effectiveness of the **Hevylite** Human IgM Kappa and IgM Lambda kits for use on the SPAPLUS.

The comparison and the validation of cut-off studies demonstrate that the results obtained on the **Hevylite** Human IgM Kappa and IgM Lambda kits for use on SPAPLUS are equivalent and the normal/abnormal outcomes determined by the reference intervals provide no adverse effects to the patient results.